



May 17, 2019

Michael Dutcher, Director
U.S. Food and Drug Administration
Minneapolis District Office
250 Marquette Avenue, Suite 600
Minneapolis, MN 55401

via email and U.S. Mail

Re: Response to Inspectional Observations; FEI Number 3015212514

Dear Director Dutcher:

Between April 10 and April 26, 2019, FDA Investigator Kellie L. Thommes performed an inspection of [REDACTED] conduct of two clinical research studies, [REDACTED] and [REDACTED] (collectively referred to as the time-to-sedation (TTS) studies) at Hennepin Healthcare System, Inc. ("Hennepin Healthcare"). Upon completion of the inspection, Ms. Thommes issued a Form FDA 483, with six inspectional observations listed.

I am responding to the Form FDA 483 with [REDACTED] for [REDACTED] Hennepin Healthcare [REDACTED]. [REDACTED] is a physician employee with [REDACTED] board certification [REDACTED] in emergency medicine [REDACTED]. [REDACTED] is an experienced physician, having practiced emergency medicine for [REDACTED] years, and [REDACTED] is a well-respected doctor who is committed to providing the best possible evidence-based care for [REDACTED] patients. [REDACTED] also conducts high-quality human subjects research and [REDACTED] is conscientious about meeting all regulatory requirements and Good Clinical Practice standards. [REDACTED] is current on all of Hennepin Healthcare's human subjects protection training requirements, including CITI training courses in Good Clinical Practice and ICH (14 modules), Primary Basic Course (10 modules), and Conflict of Interest (3 modules). [REDACTED] recently completed over 6 hours of on-site, in-person comprehensive training tailored to the needs of the Hennepin Healthcare research community, by experts in human subjects protection, law, and biomedical ethics.

As I hope this response demonstrates, everyone at Hennepin Healthcare, including [REDACTED] recognizes and understands the importance of complying with applicable human subjects protections, clinical trial-related regulatory requirements, and Good Clinical Practice generally, which safeguard both clinical trial subjects and data integrity. We

take our responsibilities to protect individuals enrolled in research very seriously. Our physicians are outstanding professionals and are required to receive extensive training in the law and ethics surrounding human subjects research before they can become investigators, and on a continuing basis. We are committed to taking all action, where appropriate, to enhance those aspects of compliance raised by the inspectional observations. In addition to our response to the observations listed on the Form FDA 483, we have included our plans to take appropriate corrective actions.

Due to the complexity of the issues identified in the Form FDA 483 and what we think may be some confusion about the TTS studies [REDACTED] conducted, we provide some critical background information before addressing each observation.

Background

At the outset, it is important to be clear that in our view, and as explained in more detail below, no patients' rights, safety, or welfare were violated due to their enrollment in the TTS studies. There were no subject deaths related to the study interventions, there were no adverse events related to the study interventions, and all subjects were treated in accord with the local¹ Emergency Medical Service (EMS) standards of care.² To be clear, the only research-related interventions in the TTS studies were:

- 1) the **use of a stopwatch** to accurately measure time from administration of a sedative to adequate patient sedation,
- 2) the **use of an agitation assessment scale** (called the Altered Mental Status Scale (AMSS)), and
- 3) **data collection forms**.

Contrary to FDA's assertions in the FDA Form 483, the drug products (Ketamine, Haloperidol, and Midazolam) administered to severely agitated persons in the community when encountered by the paramedics of Hennepin Healthcare's EMS were not study-related interventions. Instead, they are the exact treatments that are the standard of care in the prehospital setting used routinely by local EMS paramedics, and all persons treated by the Hennepin Healthcare's EMS paramedics would have received these same products to treat their severe agitation whether they were enrolled in the research or not. These drug products were administered to all patients according to the EMS Treatment Protocols and the clinical judgment of the experienced Hennepin

¹ Five EMS services operate within the County of Hennepin, and Hennepin Healthcare EMS is one of the five services. These services are collectively referred to as the "local EMS" or the "West Metro EMS."

² There are two sets of EMS Treatment Protocols. The West Metro EMS Advanced Life Support Protocols available at (<https://www.hennepin.us/-/media/hennepinus/business/work-with-hennepin-county/ems/ALS-Protocols-ver-102018.pdf?la=en&hash=ECF9D77FD626B92F3934A637EE1BB939AD2D5A07>) and Hennepin Healthcare's local EMS Treatment Protocols which are authorized by Hennepin Healthcare's EMS Medical Director (together referred to as EMS Treatment Protocols).

Healthcare EMS paramedics, which was wholly unrelated to the study itself. At no time did any patient receive drug therapy for the sake of the research.

To reiterate, all patients who received drug therapy met the criteria for sedation due to their severe and/or profound agitation when they were picked up by Hennepin Healthcare EMS's ambulance service. Both severe and profound agitation are potentially life-threatening processes, and the EMS providers are committed to accessing and treating this illness. Treating severe and profound agitation in the pre-hospital setting is very serious because both illnesses present significant potential for patient injury and complications, as well as potential provider and bystander injury. The determination to sedate a patient was based on the clinical judgment of the Hennepin Healthcare EMS paramedics at the scene and thus the determination to sedate a patient was independent from whether they were enrolled in the TTS studies, and was made prior to enrollment in the studies. Therefore, all patients received the same medical therapy and care that they would have received whether enrolled in these studies or not. So, the actual study-related interventions do not include the administration of the drug products themselves. The three study interventions listed above undeniably do not "significantly increase the risks (or decrease the acceptability of the risks) associated with the use of the drug product(s)" at issue. See 21 CFR 312.2(b)(iii).

We also note that all Hennepin EMS personnel who were involved with the TTS studies were certified paramedics. This means they have completed the most rigorous training available for emergency medical service providers nationwide and have achieved the highest level of certification required for 911 service paramedics nationally. As certified paramedics, they operate under the highest standards set forth by state statute³ and their conduct is closely overseen by the Medical Director of Hennepin Healthcare's EMS. Relevant to these studies, the EMS paramedics were authorized to administer these drug products to patients as part of the standard of care and were specifically trained in advanced airway maintenance as part of their certification requirements and as part of Hennepin Healthcare's training program for EMS paramedics.

Importantly, the overall purpose of the study was to contribute to evidence-based medicine. The specific purpose was to measure the time to sedation after administration of the available and standard of care drug products. The drug products administered by the paramedics of Hennepin Healthcare's EMS were all FDA-approved, were essentially used in accord with their labeling, were used within FDA's long-standing policy regarding the practice of medicine, and were considered the standard of care in the community. The study was not intended to be reported to FDA as a well-controlled study in support of a new indication for use or to support any other significant changes in labeling, and otherwise met the investigational new drug (IND) application exemption criteria in FDA's regulations at 21 CFR 312.2(b).

³ Minnesota Statute 144E.28.

We acknowledge that some study related documents, including the protocols for the TTS studies, were not drafted as precisely as would have been ideal. For example, the protocols do not clearly distinguish the actual study-related interventions from the standard therapies provided by Hennepin Healthcare's EMS paramedics that subjects would have received whether or not they were enrolled in the studies. This imprecise drafting could be the source of some of the FDA inspector's misperception about the sedation drugs used by the paramedics in relation to the TTS studies.

However, these drafting problems do not change the fact that the drugs were not study-related interventions. Of utmost importance, the provision of the drug therapies used was not driven by [REDACTED] research protocols. Instead, the EMS Treatment Protocols, the Treatment Protocols specific to Hennepin EMS (which are authorized by the Medical Director of Hennepin Healthcare's EMS pursuant to Minnesota Statute)⁴ and individual EMS paramedics using their clinical judgment directed whether these drug therapies were used, based on the medical conditions of their patients. [REDACTED] TTS studies are pragmatic research conducted in a real world setting that relate to standard clinical therapies, but those therapies are not research interventions. The primary endpoint in the TTS studies was time to sedation after administration of the standard therapies in an effort to contribute to evidence-based medicine in this clinical space that has a paucity of scientific validation. Under no circumstances could [REDACTED] TTS studies be considered adequate and well-controlled trials designed to evaluate the safety and effectiveness of the drug products, and they certainly were not intended to affect any regulatory decision making.

Observation # 1:

The sponsor failed to submit an IND to the FDA prior to conducting a clinical investigation with an investigational new drug.

Specifically, studies [REDACTED] and [REDACTED] were conducted without submission of Investigational New Drug (IND) applications to the FDA and do not appear to meet the IND exemption criteria, though the study was approved by the local Institutional Review Board (IRB).

Response to Observation # 1:

We strongly disagree with Observation 1 for two separate reasons: 1) the drugs at issue were not interventions in [REDACTED] studies and therefore no investigational drug products were being evaluated and 21 CFR 312 is not applicable; and 2) even if one were to accept the assertion that the drug products were research interventions, the criteria for an exemption from needing an IND at 21 CFR 312.2(b) were clearly met.

⁴ Minnesota Statute 144E.265.

1) An IND Was Not Needed Because the Drugs Were Not Research Interventions

As explained in the background discussion above, the three study-related interventions (the use of a stopwatch, the use of an agitation scale, and data collection forms) were the only departures from routine clinical care when severely agitated patients were encountered in the prehospital setting by Hennepin Healthcare's EMS paramedics.

The administration of the drug products should not be considered a research intervention for several reasons. First, the study protocols did not dictate which drugs were used for an individual patient. The Hennepin Healthcare paramedics involved in the study were clearly instructed to use the EMS Treatment Protocols as a guide and to use their discretion based on their professional medical training and judgment to determine the proper medical care of the individuals they encountered, including which drug products, if any, to administer for the initial treatment of severe and/or profound agitation. Further, the paramedics were repeatedly instructed by [REDACTED] and the EMS Medical Director that no one should be treated for sedation if such treatment was unwarranted clinically. That is, no one was to be sedated for their agitation for the sake of enrolling them in the research. The paramedics, per their training and experience, determined on their own whether or not it would be appropriate for any individual patient to be enrolled in or excluded from these studies for a variety of reasons. Moreover, use of all three drug products at issue for severe and/or profound agitation were part of the Hennepin Healthcare's EMS Treatment Protocols. The Hennepin Healthcare's EMS Treatment Protocols and the West Metro EMS Advanced Life Support Protocols represent the local standard of care used by Hennepin Healthcare and multiple other ambulance services in the area. These EMS Treatment Protocols are designed to assist EMS paramedics in determining how to handle various medical and emergency situations. They are not to be interpreted as proscriptive or determinative, but rather are intended to permit EMS paramedics to make their own clinical judgments.

Although [REDACTED] study protocols described a change in preferential initial treatment for severe and/or profound agitation based on an alteration in the Hennepin Healthcare's EMS Treatment Protocols in 6-month time intervals, this change does not mean the drug products are research-related interventions. At all times during the study, Hennepin Healthcare's EMS paramedics could have chosen not to enroll any particular patient and were free to use whichever therapy they, in their professional judgment, thought was most appropriate for the patient. Further, because Hennepin Healthcare's EMS Treatment Protocols directed this 6-month block randomization, patients received the same preferential initial treatment they would have received whether or not they were enrolled in the research. It is also within Hennepin Healthcare's discretion to choose what medical therapies are available on their ambulances at any given time, just like hospital formularies dictate the therapies available for inpatients. At all times in both TTS studies, Hennepin Healthcare EMS paramedics had at least two standard of care treatment options available for use with severely and/or profoundly agitated patients. There is certainly no requirement in any

law or regulation that all FDA-approved or standard therapies be available for patient use at all times.

2) Even If 21 CFR Part 312 Was Applicable, the Exemption Criteria Were Met

We disagree with Observation 1 that [REDACTED] failed to submit an IND to FDA prior to conducting a clinical investigation with an investigational new drug, and that the IND exemption criteria appear to not have been met. First, the products at issue should not be considered investigational new drugs. Each drug product is FDA-approved and each was essentially used in accordance with its approved labeling, and its use fell within the practice of medicine and the local standards of care.

Even if the IND regulations were applicable to the TTS studies, the use of these drug products meet the IND exemption criteria set forth at 21 CFR 312.2(b). FDA's regulations describe the five criteria that must be met for a clinical investigation of a marketed drug to be exempt from the IND requirements.

Under 21 CFR 312.2(b)(1), a clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of Part 312 when the following criteria are met:

- 1) **21 CFR 312.2(b)(1)(i)** states that the investigation cannot be intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.

This criterion is clearly met. With these investigator-initiated trials, [REDACTED] had no intention whatsoever to submit the data to FDA in support of a new indication for use nor to support any other significant changes in the labeling of these drugs. Rather, [REDACTED] was attempting to contribute to evidence-based medicine by accurately recording the time to sedation with each of these three drugs in the prehospital setting. Furthermore, the TTS studies were not designed or powered to meet FDA's regulatory requirements for data that would support changes to drug labeling.⁵

- 2) **21 CFR 312.2(b)(1)(ii)** states that if the drug that is undergoing investigation is lawfully marketed as prescription drug product, the investigation cannot be intended to support a significant change in the advertising for the product.

This criterion is met. It is undisputed that all three drugs—Ketamine, Midazolam, and Haloperidol—are all FDA-approved and lawfully marketed. Further, [REDACTED]

⁵ Of note, the TTS studies were investigator-initiated trials that were not funded by the federal government nor did they have any pharmaceutical company funding or support. Rather they were internally funded by Hennepin Healthcare.

had no intention to use the studies to support a change in advertising for the product. Rather, these trials were intended to inform clinical practice.

- 3) **21 CFR 312.2(b)(1)(iii)** states that the investigation cannot involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug products.

This criterion is also clearly met. In this instance, although the drugs were not study-related interventions, the investigators and the IRB opined that the use of the drugs for prehospital sedation was essentially in accord with their approved labeling, and that their use did not significantly increase the risk or decrease the acceptability of the risks to subjects. Similarly, all three drug products were considered to be part of the local standard of care for the Hennepin Healthcare ambulance service to use when encountering severely agitated patients in the community. Thus, the local EMS had determined that the risks associated with administering these drugs to severely agitated patients in the prehospital setting were acceptable (and were not significantly increased). Furthermore, these drugs were administered by EMS paramedics who were trained to properly evaluate their patients' medical conditions, to make professional judgments about the appropriate use of various medical therapies, to treat any related side effects, and to appropriately monitor their patients post drug administration en route to the hospital.

- a) Specifically, Haloperidol is indicated for schizophrenia and control of ticks and vocal utterances associated with Tourette's disorder.⁶ It is used routinely for persons with agitation from these and other conditions in various hospital and prehospital settings. It does contain a black box warning regarding increased mortality in elderly patients with dementia related psychosis and it can cause, among others, cardiac-related side effects. However, Haloperidol is an old drug with a well-known safety profile from extensive post-market use, and the use in patient care by Hennepin Healthcare's EMS is generally consistent with the indications and risk profile.
- b) Next, Ketamine is indicated for the induction of anesthesia and as an anesthetic agent.⁷ The label states that cardiac function should be monitored and respiratory depression may occur with overdosage or too rapid a rate of administration. Ketamine is also routinely used as a sedative in various hospital and prehospital settings. Its use by Hennepin EMS paramedics, again, is generally consistent with the labeled indications and risk profile.

⁶ See, e.g., Haloperidol Lactate Injection Prescribing Information, <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8397a841-f240-4767-9dcd-781e6d3f7c7f>.

⁷ See, e.g., Ketamine Hydrochloride Injection Prescribing Information, <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=58487c78-a641-4278-acc0-343596ee8683>.

- c) Last, Midazolam is labeled for use in sedation and induction of anesthesia.⁸ Its labeling contains a boxed warning stating that its use can be associated with respiratory depression and respiratory arrest. Thus, the label recommends continuous monitoring of patients post-administration of the drug. Midazolam is routinely used as a sedative in various hospital and prehospital settings. The use by Hennepin Healthcare's EMS paramedics is consistent with the indications, risk profile, and available safety monitoring.

The use of these products is generally consistent with their approved labeling and standards of care across the country, which is supported by peer-reviewed medical literature. See Appendix 2 for a bibliography of references for each drug product. Next, as explained, the Hennepin Healthcare EMS paramedics are skilled professionals who are rigorously trained and experienced in maintaining a patient's airway, supporting ventilation, and continuously monitoring patients who have received these drugs. For all the reasons articulated above, we do not believe that using these drugs to treat severely agitated patients in the prehospital setting constitutes a significantly increased risk or a decrease in the acceptability of the risks associated with the use of these drugs.

- 4) **21 CFR 312.2(b)(1)(iv)** states that the investigation must be conducted in compliance with the requirements for institutional review set forth in Part 56 and with the requirements for informed consent in Part 50.

This criterion is also met. First, an appropriately constituted and properly registered IRB reviewed and approved the protocols under appropriate review procedures. Next, the IRB did not require informed consent from the participants because it determined that a waiver of informed consent was appropriate under 45 CFR 46.116(d). While FDA's regulations do not currently contain a similar provision for waiver of informed consent, it is consistent with current FDA policy. FDA issued an enforcement discretion guidance in 2017⁹ describing its intention not to object to an IRB's waiving or altering of informed consent requirements for certain minimal risk clinical investigations that are important to address public health needs and that do not compromise the rights, safety, or welfare of human subjects. FDA issued this guidance as an interim measure while it promulgates regulations that reflect the statutory authority granted to FDA by the 21st Century Cures Act, which explicitly permits an exception from the informed consent requirements for such clinical trials.¹⁰ In the guidance, FDA states "until FDA

⁸ See, e.g., Midazolam Hydrochloride Injection Prescribing Information, <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=737361a0-8db1-4d3c-ba5e-44df3f49fa22>.

⁹ Food and Drug Administration, *Guidance for Sponsors, Investigators, and Institutional Review Boards – IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects* (July 2017), <https://www.fda.gov/media/106587/download>.

¹⁰ On December 13, 2016, the 21st Century Cures Act (Cures Act) (P.L. 114-255) was signed into law. Title III, section 3024 of the Cures Act amended sections 520(g)(3) and 505(i)(4) of the FD&C Act to

promulgates these regulations we do not intend to object to an IRB approving a consent procedure that does not include or that alters some or all of the elements of informed consent set forth in 21 CFR 50.25 or waiving the requirements to obtain informed consent when the IRB finds and documents that” the four provisions in 45 CFR 46.116(d) listed above are met.¹¹ In late 2018, FDA issued a Federal Register notice stating its intention to promulgate regulations that would allow for the waiver of informed consent when a clinical investigation poses no more than minimal risk to human subjects.¹² As the TTS studies both involved study interventions that are no more than minimal risk (i.e. the use of a stopwatch, an agitation scale, and data collection forms) and met the criteria for a waiver of informed consent, the IRB clearly acted appropriately in not requiring informed consent from the study participants.

In addition, Hennepin’s Healthcare’s IRB further protected the subjects enrolled in these studies by requiring the investigators to provide them, when possible, pertinent information about the trials and their enrollment. And, in the [REDACTED] study, subjects were given the opportunity to have their data removed from the research database if they chose.

The understanding of the IRB and the investigator that the IND exemption criteria were met is supported by a letter from the Director of the Division of Psychiatry Products at the Center for Drug Evaluation and Research (CDER) dated April 10, 2014, which stated that the Agency found that a trial involving Ketamine and Haloperidol in the pre-hospital setting to evaluate time to sedation in agitated patients was IND exempt. That study was very similar in design to the TTS studies, and the patient population described in the IND application submitted by [REDACTED] at that time was identical to the patient populations studied in the TTS studies. Thus, the investigator and the IRB appropriately concluded the use of the marketed drug products in the studies did not alter the risk calculus and no IND was needed.

- 5) **21 CFR 312.2(b)(1)(v)** states that the investigation must be conducted in compliance with the requirements of 21 CFR 312.7.

This requirement is also met. 21 CFR 312.7 prohibits preapproval promotion of investigational drug products. Under this regulation, an investigator cannot represent in a promotional context that an investigational new drug is safe or

provide FDA with the authority to permit an exception from informed consent requirements when the proposed clinical testing poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of the human subject. The “Cures Act” can be accessed at:

<https://www.gpo.gov/fdsys/pkg/PLAW-114publ255/pdf/PLAW-114publ255.pdf>

¹¹ Food and Drug Administration, *Guidance for Sponsors, Investigators, and Institutional Review Boards – IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects* at 4 (July 2017), <https://www.fda.gov/media/106587/download>.
12 83 FR 57378 (Nov. 15, 2018).

effective for the purposes for which it is under investigation or otherwise promote the drug. In this instance, the drug products at issue were all FDA-approved, were not study related interventions, and were used within the practice of medicine and local standards of care. Furthermore, [REDACTED] did not engage in any promotional activities nor represent that these drugs were safe or effective for an unapproved use.

Corrective Actions Related to Observation # 1:

The FDA inspector may have incorrectly concluded that an IND was necessary and/or that the IND exemption appeared to not have been met due to some imprecise language in the TTS protocols. Therefore, we have taken the following corrective actions:

- 1) We have implemented the required use of a standardized protocol template for every submission of an investigator-initiated study to the IRB, and rejection by the IRB of all investigator-initiated submissions which do not follow the template and/or are otherwise incomplete. We believe that the use of the protocol template will help investigators be more accurate and complete in the descriptions of their studies.
- 2) On May 7 and 8, 2019, an on-site, mandatory comprehensive retraining for all investigators was provided.¹³ This training was designed to meet the specific needs and research interests of Hennepin Healthcare. The training addressed, among other topics, FDA regulatory requirements to INDs, Investigational Device Exemptions (IDEs), Good Clinical Practice, research ethics, and clinical research including the use of investigational products. [REDACTED] participated in person at both training sessions totaling approximately 6 hours.
- 3) Out of an abundance of caution, we are establishing a policy of mandatory pre-review which will be coordinated by Hennepin Healthcare's Office of Education and Quality in Clinical Research for all Full Committee IRB submissions that involve an investigator-initiated clinical research proposal, which will include an assessment of whether an IND or Investigational Device Exemption (IDE) may be needed prior to submission to the IRB.

Observation # 2:

Legally effective informed consent was not obtained from a subject or a subjects' legally authorized representative and the situation did not meet the criteria in 21 CFR 50.23 and 50.24 for exception.

Specifically, subjects were enrolled in studies [REDACTED] and [REDACTED] without obtaining informed consent from the subjects or their legally authorized representatives; neither study appeared to meet criteria for exception from informed

¹³ Investigators unable to attend in person will be required to view the recorded version and all investigators were provided access to the training materials.

consent, though the studies were approved by the local IRB.

Response to Observation # 2:

We do not agree that informed consent was required to be obtained from the subjects in the TTS studies. Rather, the IRB's decisions to waive informed consent under 45 CFR 46.116(d) in the TTS studies was justified, and was in accord with FDA's current pronouncements on the applicability of the use of this waiver for FDA-regulated studies. Observation 2 mentions two exceptions from informed consent at 21 CFR 50.23 and 21 CFR 50.24 that are currently allowable for use under FDA's regulations and notes that those provisions are not applicable in this instance. However, Observation 2, does not appear to take into account FDA's current policies regarding the waiver of informed consent including its statement of intent to promulgate regulations that adopt 45 CFR 46.116(d) into FDA's regulations. Thus, we contend that the requirement to obtain informed consent was properly waived by the IRB. Furthermore, as described below, the IRB appropriately determined that the waiver of informed consent criteria in 45 CFR 46.116(d) were met.

Waiver of Informed Consent Was Appropriate

45 CFR 46.116(d) lists four criteria that must be met for the waiver of informed consent:

- a) the research involves no more than minimal risks to the subjects;
- b) the waiver will not adversely affect the rights and welfare of the subjects;
- c) the research could not practicably be carried out without the waiver;
- d) whenever appropriate the subjects will be provided with additional pertinent information after participation.

We address each of these in turn:

- a) The Research Involves No More than Minimal Risk:** The waiver of the informed consent requirements at 45 CFR 46.116(d) is only applicable to studies that are considered to be minimal risk. Minimal risk studies are defined by regulation as those where "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests".¹⁴

In these studies, the principal investigator, [REDACTED] and the IRB believed that the study-related interventions involved: 1) the use of a stop watch to accurately measure the time to sedation after administration of the sedative; 2) the use of

¹⁴ See 21 CFR 50.3(k) and 45 CFR 46.102(j).

the AMSS scale to assess the individual's level of agitation; and, 3) the collection of various data points. This determination led them to conclude that the incremental risks of the study interventions, as compared with the risks of the treatments that the individuals would have received as patients in the pre-hospital setting, involved no more than minimal risk. This is an appropriate interpretation of the regulations for several reasons described below.

First, the IRB regulations at 21 CFR 56.111(a)(2) state that for approval the “risks to subjects [must be] reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research)” In fact, the Department of Health and Human Services’ (DHHS) Office of Human Research Protections (OHRP) issued a draft guidance document in 2014 on disclosing reasonably foreseeable risks in research evaluating standards of care.¹⁵ In this document OHRP explains its position that “in general the *reasonably foreseeable risks of research* in a study include the already identified risks of the standards of care being evaluated as a purpose of the research when the risks being evaluated are different from the risks some of the subjects would be exposed to outside of the study.”¹⁶ OHRP clarified that if the research is designed to evaluate the risks of the standards of care, or to ascertain the existence, extent or nature of a particular harm then those risks should be disclosed.

In contrast, the TTS studies were designed such that the risks individuals were exposed to as part of the studies were no different from the risks they were exposed to from treatment outside the research; and, although data about any complications of medication use were collected in these studies, the primary outcome of each study was time to adequate sedation, not safety. Hence, based on FDA's regulation and OHRP's guidance, the principal investigator and the IRB believed that the drugs themselves should not be considered study-related interventions. Therefore, the risks of these studies were determined only on the basis of the limited minimal risk study interventions (i.e., use of a stop watch and the AMSS, and data collection) and not the drug products themselves.

b) The waiver will not adversely affect the rights and welfare of the subjects:

During the conduct of these studies, the patients who presented to the ambulance service with severe and/or profound agitation would have received

¹⁵ Office for Human Research Protections, Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care (Mar. 2016), <https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-disclosing-risk-in-standards-of-care/index.html>

¹⁶ *Id.*

the same exact medical therapies for sedation in the pre-hospital setting whether or not they were enrolled in the study. The drug treatments that the patients received (i.e. Haloperidol, Midazolam, and Ketamine) constitute the local standards of care in the community in emergency settings and those medical standards were not deviated from in any way for the purposes of the research. And as previously mentioned, all Hennepin Healthcare EMS paramedics were instructed to consider the EMS Treatment Protocols and to use their clinical judgment when making individual treatment decisions.

Further, based on the patient's medical condition when encountered by the ambulance service in the prehospital setting (i.e. presenting with severe and/or profound agitation), such patients would have been unable to consent to clinical care. In clinical scenarios such as this where there is an out-of-the-hospital emergency and time to treatment is critical, obtaining consent is not an ethical requirement. Rather, it is most important to act in the patient's best interest and to provide appropriate care according to standard treatment protocols. Similarly, due to the nature of the patient's medical condition at the time of enrollment by the paramedics on the scene, it would have been infeasible to obtain consent to participate in this minimal risk research.¹⁷ Thus, we do not believe that the rights and welfare of the subjects were adversely affected by the use of the waiver.

c) The research could not practicably be carried out without the waiver:

Because the participants were severely and/or profoundly agitated, a condition that is potentially a medical emergency, and needed urgent intervention in the form of medical sedation by EMS paramedics, they could not have provided legally effective informed consent to participate. Similarly, subjects' legally authorized representatives were not typically available to provide consent and/or the rapidity with which treatment must be administered in the prehospital setting precluded the ability to obtain informed consent.¹⁸ Therefore, the research could not practicably have been carried out without the waiver.

d) Whenever appropriate the subjects will be provided with additional pertinent information after participation:

The IRB specifically required that the subjects who were enrolled in the TTS studies received notification of enrollment once they were no longer incapacitated and could make decisions themselves. At that time, the subjects were provided with additional pertinent information. And, for [REDACTED] subjects were also given an opportunity to request their data be removed from the study database if they wished.

¹⁷ See generally M. Martel et al., A Brief Assessment of Capacity to Consent Instrument in Acutely Intoxicated Emergency Department Patients, 36 AM. J. OF EMERGENCY MEDICINE 18 (Jan. 2018).

¹⁸ [REDACTED]

As explained above in response to Observation 1, while FDA's regulations do not currently contain a provision similar to 45 CFR 46.116(d) for waiver of informed consent, FDA has issued an enforcement discretion guidance¹⁹ describing its intention not to object to an IRB's waiving or altering of informed consent requirements for certain minimal risk clinical investigations that are important to address public health needs and that do not compromise the rights, safety, or welfare of human subjects.²⁰ FDA also has issued a Federal Register Notice describing its intention to adopt a waiver of informed consent provision in line with 45 CFR 46.116(d).²¹

We also note that in an article published in 2015, FDA senior leadership and other thought leaders called for FDA to “establish a risk-based approach to obtaining informed consent in [pragmatic clinical trials] that would facilitate the conduct of [pragmatic clinical trials] without compromising the protection of enrolled individuals or the integrity of the resulting data.”²² The authors, which included FDA officials, expressed concern “that current FDA requirements for obtaining individual informed consent may deter or delay the conduct of pragmatic clinical trials intended to develop reliable evidence of comparative safety and effectiveness of approved medical products that are regulated by the FDA.”²³ The design and intent of these TTS studies were consistent with these forward-thinking principles.

Corrective Actions Related to Observation # 2:

As [REDACTED] and the IRB appropriately analyzed and applied the waiver of informed consent criteria, no corrective actions are planned with regard to Observation 2.

Observation # 3:

An investigation was not conducted in accordance with the investigational plan.

Specifically,

- a. Serious Adverse Events (SAE) were not reported in a timely fashion to the IRB as required by the Institutional Review Board (IRB) written procedures and IRB study approval letters. IRB written procedure Attachment EEE requires all

¹⁹ Food and Drug Administration, *Guidance for Sponsors, Investigators, and Institutional Review Boards – IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects* (July 2017), <https://www.fda.gov/media/106587/download>.

²⁰ As part of the federal efforts to facilitate evidence-based medicine through comparative effectiveness research, in 2014 the Department of Health and Human Services issued draft guidance, “Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care”. Office for Human Research Protections, *Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care* (Mar. 2016): <https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-disclosing-risk-in-standards-of-care/index.html>.

²¹ 83 FR 57378 (Nov. 15, 2018).

²² ML Anderson et al., *The Food and Drug Administration and pragmatic clinical trials of marketed medical products*, 12 CLINICAL TRIALS 511 (2015).

²³ *Id.*

serious adverse events related to the study treatment (or more likely related than unrelated), be reported within five working days of knowledge of the event.

(specific examples listed in 483 omitted here)

- b. All study activities required by the study plans were not done as follows: (specific examples listed in 483 omitted here).
- c. Deviations listed in the paragraphs above were not reported in the Annual Re-approval Continuing Review Reports as required by the IRB written procedure Attachment EEE, which requires any protocol deviation in which there is only minimal risk to the subject or others be reported on the next Annual Re-approval Continuing Review Report. No deviations were reported in the annual reports submitted by [REDACTED] to the IRB for either study [REDACTED] or [REDACTED].

Response to Observation # 3:

We do not agree with Observation 3 as it is based on the false premise that the drug therapies provided to patients as part of standard of care by Hennepin Healthcare EMS paramedics, were study-related interventions. Observation 3a alleges that SAEs were not reported in accordance with IRB written procedures and IRB approval letters. However, there were no SAE's that occurred during the TTS studies that were related to the actual study interventions (the use of the stopwatch, the agitation scale, and the data collection). Therefore, all of the examples of alleged failures listed in Observation 3a were related to the drug products administered to patients as part of their pre-hospital clinical care and were not related to the study interventions, and therefore were misidentified as SAEs that were improperly documented and reported.

We acknowledge that [REDACTED] in some communications to the IRB and a clinical monitor mistakenly attributed adverse events related to the drug products to the study related interventions in [REDACTED] TTS studies. This confusion arose because the data collection forms for the TTS study captured follow-up information about the subject's medical care. The collection of these adverse events, while not a primary study outcome, seemed appropriate at the time to collect in order to have a more fulsome picture of a patient's experiences with the drug products to serve as descriptive information in any publications about the TTS studies. In retrospect, [REDACTED] should have been more clear in both [REDACTED] communications to the IRB and the clinical monitor, and in [REDACTED] publication²⁴ about which outcomes were attributed to the study interventions and which were related to standard care. Observation 3b describes a variety of irregularities with regard to study conduct and documentation. We acknowledge that these missing data points should have been properly recorded. However, these

omissions did not directly affect the safety and welfare of any enrolled subjects.

Observation 3c explains that these protocol deviations were not reported to the IRB in the required Annual Re-approval Continuing Review Reports for both [REDACTED] and [REDACTED]. We acknowledge that [REDACTED] should have reported these lapses in documentation which constituted protocol deviations to the IRB on the required forms annually. However, these omissions did not directly affect the safety and welfare of any enrolled subjects.

Corrective Actions Related to Observation # 3:

- 1) To ensure that [REDACTED] and other investigators at Hennepin Healthcare do not conflate research-related risks with the risks associated with the provision of standard of care therapies, we are requiring the use of a protocol template for IRB submissions for investigator-initiated studies that requires a clear delineation between research interventions and standard medical therapy. This protocol template will thus eliminate the confusion surrounding which adverse events are attributable to the study interventions and which are not.
- 2) To ensure that [REDACTED] and other investigators at Hennepin Healthcare more carefully and accurately record study-related data and report any protocol deviations to the IRB as required by the IRB's written procedures and forms, we required re-training of all Hennepin Healthcare investigators on Hennepin Healthcare's IRB policies and the importance of proper data collection and reporting. The training was held on May 7 and 8, 2019, and included a segment that was designed to help ensure proper adherence to the protocol and data integrity.
- 3) Hennepin Healthcare and [REDACTED] agree that for each study that [REDACTED] serves as the principal investigator [REDACTED] will be assigned a Research Monitor to review the protocol and case report forms to ensure they properly characterize the study interventions and any related adverse events, and then to oversee the conduct of the trials including specific monitoring for accurate and complete record keeping for a period of 2 years.

Observation # 4:

Failure to ensure proper monitoring of the study.

Specifically, the sponsor did not ensure appropriate monitoring was performed of studies [REDACTED].

Response to Observation # 4:

We do not agree with Observation 4 and note that it appears to be deficient. It does not contain sufficient detail to understand any lack of proper monitoring and for Hennepin to

properly respond to this observation.

As discussed in response to Observation 1, the TTS studies were IND exempt based on 21 CFR 312.2(b) and therefore the regulatory requirements related to sponsor and investigator monitoring at 21 CFR 312.50 and 21 CFR 312.60 are not applicable. However, we do acknowledge that proper monitoring and oversight is essential for appropriate human subjects protections and data integrity, and compliance with the protocol, Good Clinical Practice, and applicable regulatory requirements.²⁵

Looking to FDA for guidance in this space, we note that FDA's guidance on "Oversight of Clinical Investigations – A Risk Based Approach to Monitoring" makes clear that "the regulations are not specific about how sponsors are to conduct such monitoring and are therefore compatible with a range of approaches to monitoring that will vary depending on multiple factors."²⁶ The guidance also states that "FDA recommends that each sponsor design a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial."²⁷ In these studies, as the study-related interventions (use of a stop watch, an agitation scale, and data collection forms) are not associated with safety concerns, using a risk-based approach, the monitoring would be relatively limited. With regard to human subjects protection-related monitoring, [REDACTED] and [REDACTED] research team made sure to provide proper information about the studies when subjects were no longer incapacitated. With regard to data integrity risks, [REDACTED] reviewed the study documentation records as appropriate. [REDACTED] regularly met with the research coordinators, directly supervised data collection at random intervals, regularly reviewed study records, provided EMS paramedics with frequent opportunities to discuss the study with [REDACTED] in person, and, with the aid of co-investigators, performed several interim analyses.

Although the drugs used for sedation were not study-related interventions, we also note that there were various clinical monitoring procedures in place for all patients brought to the hospital by ambulance by the highly-trained and experienced EMS paramedics, by Hennepin Healthcare EMS management, and by Emergency Department and other hospital personnel.

Corrective Actions Related to Observation # 4:

Due to the lack of specificity with regard to Observation 4 and the relative safety of the study-related interventions, no corrective actions are planned in response to

²⁵ The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) also recommends a risk-based approach. ICH, *Guideline For Good Clinical Practice E6(R1)* at 26 (June 10, 1996), https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

²⁶ Food and Drug Administration, *Guidance for Industry – Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring* at 2 (Aug. 2013), <https://www.fda.gov/media/116754/download>.

²⁷ *Id.* at 10.

Observation 4.

Observation # 5:

Investigational drug disposition records are not adequate with respect to dates, quantity and use by subjects.

Specifically, no clinical investigator-required investigational drug use and disposition records were maintained for studies [REDACTED].

Response to Observation # 5:

Observation 5 is based on the incorrect premise that the drug products that were administered clinically to patients as part of their standard care were study-related interventions, and therefore 21 CFR 312.62(a), which requires investigators to maintain drug disposition records, is not applicable. But even if FDA considers the drug products to be investigational new drugs as used in the ED by its emergency medicine physicians, this regulation regarding drug disposition records would still be inapplicable as the TTS studies are IND-exempt under 21 CFR 312.2(b).

Thus, [REDACTED] was not required to maintain drug use and disposition records. Instead, because the drug products were administered according to the Hennepin Healthcare EMS Treatment Protocols and Hennepin Healthcare EMS paramedics' clinical judgment, Hennepin Healthcare EMS personnel maintained this information in their version of an electronic medical record, called SafetyPAD, as per routine.

We also note that the fact that the three drug products were obtained for patient use from each ambulance's regular stock of drug products, is further evidence that the drug products were not study related interventions. Accordingly, Hennepin Healthcare's EMS did not purchase drug supplies for the ambulances specific to these research studies.

Corrective Actions Related to Observation # 5:

No corrective actions are planned in response to Observation 5.

Observation # 6:

Not all changes in research activity were approved by an Institutional Review Board prior to implementation.

Specifically, the study [REDACTED] was suspended and study related personnel were instructed to use the standard Advanced Life Support protocols during the approximately two week period surrounding the 2018 Super Bowl that was held in Minneapolis, MN, without approval from the IRB prior to implementation.

Response to Observation # 6:

Observation 6 is based on the incorrect premise that the drug products that were administered clinically to patients as part of their standard care were study-related interventions, and the incorrect view that an IND was needed to conduct this study which would have made 21 CFR 312.66 applicable.

At the outset, we note that under Minnesota law, the Medical Director of Hennepin Healthcare EMS had the explicit authority to alter Hennepin Healthcare EMS Treatment Protocols.²⁸ The Medical Director did alter the Hennepin Healthcare EMS Treatment Protocols via email communication to the Hennepin Healthcare EMS paramedics on January 25, 2018. In that email, it was communicated that the paramedics should not enroll subjects during the time period from January 26, 2019 to approximately February 6, 2019. Such a temporary pause in enrollment would not be considered “a change in research activity” required to be reported to the IRB under 21 CFR 312.66 and this did not constitute a suspension of IRB approval under 21 CFR 56.108(b). It is common for investigators to have temporary pauses in study enrollment for a variety of reasons, such as illness, vacation, or conference attendance. While [REDACTED] used the term “suspension” (that was captured in the Medical Director’s email), [REDACTED] meant it in the colloquial sense of the word and did not mean to suggest that the study itself was actually suspended by the IRB, nor did [REDACTED] mean that there was an actual change to the research. Out of an abundance of caution, the communication to the Hennepin Healthcare EMS paramedics simply was intended to pause enrollment during the busy and unpredictable Super Bowl time period when there may have been an increased need for EMS services.

We also note that this pause in enrollment did not compromise patients’ safety, rights, or welfare in any possible way as all patients were treated according to the usual EMS Treatment Protocols during the Super Bowl time period. Further, no data integrity risks could have arisen as no patients were enrolled as subjects during this time.

Corrective Actions Related to Observation # 6:

No corrective actions are planned in response to Observation 6.

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With respect to the Corrective Action Plans for Observation # 1 and Observation # 3, we plan to provide a written update describing our progress in meeting those obligations to FDA in 6 months, at 1 year, and upon full completion. We hope this response adequately addresses the inspectional observations and conveys to you the importance we place on compliance with the applicable regulatory requirements governing clinical research and informed consent.

²⁸ 2017 Minnesota Statute 144E.265, subd.2.

Lastly, given the complexities of these studies and the apparent confusion of the FDA inspector about our standard clinical practices, we respectfully request to open a dialogue between Hennepin Healthcare and Agency officials to discuss our responses to the inspectional observations. We would welcome the opportunity to meet with Dr. Janet Woodcock, Dr. Robert Temple, Mr. Donald Ashley, Dr. David Burrows, and Ms. Melinda Plaisier.

Thank you for your consideration of our response. Please contact me at [REDACTED] if you need additional information or have any questions.

Sincerely,

[REDACTED]
Hennepin Healthcare [REDACTED]

[REDACTED]
Core Faculty Physician
Department of Emergency Medicine
Hennepin Healthcare System, Inc.

[REDACTED]
Enclosures:
[REDACTED]

Appendix 2—Bibliography of References

CC: Dr. David Burrow, Director, Office of Scientific Investigations, Office of Compliance, CDER

Mr. Donald Ashley, Director, Office of Compliance, CDER

Appendix 2

Bibliography of References

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